

Reversible O–O Bond Cleavage in Copper–Dioxygen Isomers: Impact of Anion Basicity

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μ - η^2 : η^2 -peroxodicopper(II) (**P**) and bis(μ -oxo)dicopper(III) (**O**) complexes are valence isomers that differ by the degree of O₂ reduction and the presence of an O–O bond.^{1,2} These isomers can exist in a measurable equilibrium with a small activation energy.^{3–6} This facile isomerization is significant to the processes of making and breaking an O–O bond, which are key steps in photosynthesis, respiration, and the catalytic cycle of tyrosinase, a binuclear copper enzyme that *ortho*-hydroxylates phenols. The characterized **P** species of oxygenated tyrosinase is accepted as the active oxidant in the oxygen atom transfer reaction, but a transient **O**-type species in which the O–O bond is cleaved prior to oxygen insertion cannot be overlooked.⁷ Understanding these steps in detail is important to the design of synthetic catalysts that use O₂ as a terminal oxidant.

A systematic study of the influence of the Lewis basicity of various anions, that is, their coordinating ability, on the **P**/**O** equilibrium was undertaken as a model of substrate binding to the **P** core in tyrosinase.^{5,6} **P**/**O** mixtures were prepared with the ligand *N,N,N',N'*-tetraethylpropane-1,3-diamine (TEPD) by injecting a CH₂Cl₂ solution of [(TEPD)₂Cu(CH₃CN)_{*n*}](X), where X[–] = SbF₆[–], CF₃SO₃[–], TsO[–] (*p*-toluenesulfonate), or CH₃SO₃[–],⁸ into a pre-cooled, preoxygenated volume of CH₂Cl₂, tetrahydrofuran (THF), or acetone (–85 °C, 1 atm O₂, 1 mM in Cu). **P** and **O** isomers were stable only below –75 °C and were identified by their characteristic charge-transfer absorptions (Table 1 and Figure 1).¹ In THF or CH₂Cl₂, [(TEPD)₂Cu₂O₂](CF₃SO₃)₂ exhibits rapid, reversible interconversion between equilibrium positions upon temperature change.⁹ A van't Hoff analysis yields $\Delta H^\circ = -4.3(2)$ kJ mol^{–1} and $\Delta S^\circ = -24(2)$ J K^{–1} mol^{–1} for this **P** ⇌ **O** equilibrium in THF: **O** is favored enthalpically and **P** is favored entropically, as previously determined for other systems.^{4,5}

More strongly coordinating counteranions bias the **P**/**O** equilibrium position toward **P**, from ~10:90 with SbF₆[–] to ~100:0 with CH₃SO₃[–] (Figure 1a). The **P**/**O** ratio follows anion basicity regardless of size; for example, CH₃SO₃[–] is slightly smaller than CF₃SO₃[–], yet the more compact **O** isomer is not observed with CH₃SO₃[–]. Such a basicity effect is counter-intuitive, as more electron donation to the Cu₂O₂ core is anticipated to stabilize the higher oxidation state of the copper centers and hence favor the **O** isomer.¹⁰

Titration experiments with competing anions highlight the importance of anion basicity and reveal the existence of specific anion/dication interactions. Addition of a more coordinating anion Y[–] (CF₃SO₃[–], TsO[–], CH₃SO₃[–], CF₃CO₂[–], PhCO₂[–]) to a preformed **P**/**O** solution with a “weaker” anion X[–] (SbF₆[–], CF₃SO₃[–]) results in a rapid, isosbestic isomerization in the direction **O** → **P**. Spectroscopically pure **P** species are obtained by addition of 1.0 equiv of TsO[–], CH₃SO₃[–], CF₃CO₂[–], or PhCO₂[–] per binuclear complex (Figure 1b).^{6,11} In all cases, no significant spectral changes

Scheme 1. Equilibrium between TEPD-Based **P** and **O** Species

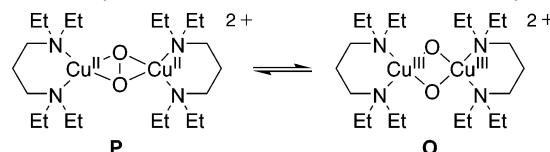


Table 1. [(TEPD)₂Cu₂O₂](X)₂ Solutions: UV–Vis Features and **P**/**O** Ratios

X [–]	solvent	P : O ^a	UV–Vis Features: λ , nm (ϵ , mM ^{–1} cm ^{–1}) ^b			
			O	P	O	P
SbF ₆ [–]	THF	10:90	326 (12)	~360 (sh)	422 (23)	
CF ₃ SO ₃ [–]	THF	50:50	~320 (sh)	363 (16)	416 (13)	605 (0.5)
TsO [–]	THF	100:0 ^c		363 (26)		636 (1.3)
CH ₃ SO ₃ [–]	THF	100:0 ^c		362 (28)		640 (1.1)
CF ₃ CO ₂ ^{–d}	THF	100:0 ^c		364 (20)		660 (1.2)
PhCO ₂ ^{–d}	acetone	100:0 ^c		362 (21)		690 (1.0)

^a Approximate **P**/**O** ratio at –85 °C, estimated from the average molar extinction coefficients of the 360 and 400 nm bands (26 and 24 mM^{–1} cm^{–1}, respectively).¹ ^b A weak band is also present at ~500 nm for the **P** species (Figure 1a); sh = shoulder. ^c At the experimental detection limit (<5% in **O**). ^d Solutions formed by titration (see text).

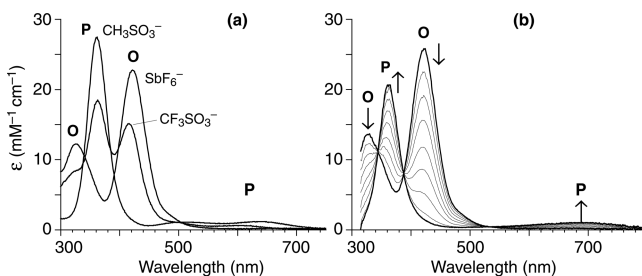


Figure 1. (a) UV–vis spectra of [(TEPD)₂Cu₂O₂](X)₂, with X[–] = SbF₆[–], CF₃SO₃[–], and CH₃SO₃[–] in THF at –85 °C. (b) Addition of [N(*n*-Bu)₄](PhCO₂) (0–0.9 equiv per dicopper species) to an acetone solution of [(TEPD)₂Cu₂O₂](CF₃SO₃)₂ at –87 °C.¹¹

occur upon addition of more than 1.0 equiv of Y[–] per Cu₂O₂ species, and the final **P**/**O** ratio is the same as that per direct oxygenation of [(TEPD)₂Cu(CH₃CN)_{*n*}](Y) (Y[–] = CF₃SO₃[–], TsO[–], or CH₃SO₃[–]). In contrast, the reverse titration of a [(TEPD)₂Cu₂O₂](Y)₂ solution with a weaker X[–] anion is incomplete even with 200 equiv of X[–] per dimer.¹² Overall, these experiments suggest that each dicationic Cu₂O₂ species is associated with *one* anion intimately.¹³

Extended X-ray Absorption Fine Structure (EXAFS) analysis of a frozen THF solution of [(TEPD)₂Cu₂O₂](CH₃SO₃)₂ provides structural evidence of the close association between the anion and the Cu₂O₂ core in this spectroscopically pure **P** species. The EXAFS data are consistent with a side-on peroxo-bridged copper dimer having four Cu–N/O¹⁴ interactions at 1.94 Å, one Cu–O at 2.26 Å, and one Cu···Cu at 3.51 Å (Figure 2a).¹ The scattering atom at

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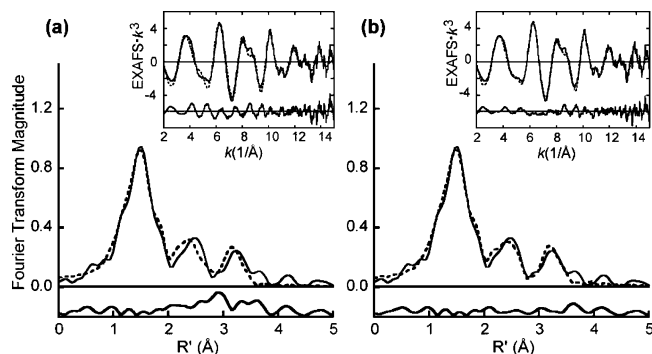


Figure 2. EXAFS data (inset) and Fourier transforms with offset fit residuals (bottom) of $[(\text{TEPD})_2\text{Cu}_2\text{O}_2](\text{CH}_3\text{SO}_3)_2$ (—). (a) 4-component fit (---); (b) 5-component fit (---): 4 Cu–N/O = 1.94 Å, 1 Cu–O = 2.26 Å, 6 Cu···C = 2.88 Å, 1 Cu···S = 3.47 Å, 1 Cu···Cu = 3.51 Å.

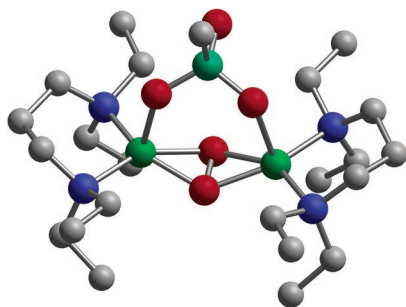


Figure 3. DFT-optimized geometry of $\{[(\text{TEPD})_2\text{Cu}_2\text{O}_2](\text{CH}_3\text{SO}_3)_2\}^+$. Cu–O_{eq} = 1.94 Å (avg), Cu–N = 2.02 Å (avg), Cu–O_{ax} = 2.26 Å, Cu···C = 2.87 Å (avg), Cu···S = 3.36 Å, and Cu···Cu fixed to 3.51 Å.

2.26 Å is required for a good fit and is ascribed to a CH_3SO_3^- oxygen atom,¹⁵ consistent with the titration experiments. Coordination of CH_3SO_3^- would place the sulfur atom within 3.3–3.8 Å of the copper centers, which corresponds to the poorly fitted region in the 4-component model. A 5-component EXAFS fit with a Cu···S interaction at a refined distance of 3.47 Å¹⁶ provides a better match to the data (Figure 2b, Table S1). The dual requirement for a Cu–O interaction at 2.26 Å and a Cu···S interaction at 3.47 Å in the EXAFS fit establishes that the CH_3SO_3^- anion is well-ordered at close range from the Cu_2O_2 core.

Density Functional Theory (DFT) calculations¹⁷ support the EXAFS structure. A plausible model consists of the association between a $[(\text{TEPD})_2\text{Cu}_2\text{O}_2]^{2+}$ molecule and one CH_3SO_3^- anion, in accord with the experimental 1:1 anion-to-dimer stoichiometry. Electronic optimization of this model with a Cu···Cu distance fixed to the experimental value of 3.51 Å converges to the **P** species depicted in Figure 3. The CH_3SO_3^- anion bridges the two copper(II) ions through axial positions, a ligation mode documented for the weaker CF_3SO_3^- anion in copper dimers.¹⁸ The calculated distances about the copper ions agree closely with the EXAFS results, notably for the axial oxygen atoms. The Cu_2O_2 core exhibits a slight butterfly distortion with a dihedral angle of $\sim 150^\circ$ between the two CuO_2 planes that may account for the weak feature at ~ 500 nm in the UV–vis spectrum of this **P** species (Figure 1a).¹⁹

The axial ligation mode of the anion is substantiated experimentally. The ~ 600 nm charge-transfer feature of the **P** isomers shifts to lower energies by 12% as the basicity of the counteranion increases from CF_3SO_3^- to PhCO_2^- (Table 1). Since this transition originates from the *out-of-plane* π^* orbital of the peroxy moiety, this large shift strongly suggests that the anion is positioned above the Cu_2O_2 plane. This indirect characterization of the anion–core association may become useful for probing substrate binding to a **P** core.

In conclusion, axial binding of an anion induces an electronic/electrostatic, not steric, preference for the **P** isomer; the O–O bond is not cleaved with an anion positioned axially on the Cu centers. In oxytyrosinase, although the substrate presumably approaches the **P** core from above,²⁰ its subsequent deprotonation yields a phenolate anion, which is much more basic than the anions used here. Such a strong ligand can potentially redefine the equatorial planes of the copper centers with minimal reorganization of the O_2 -derived ligands. Such change could trigger O–O bond cleavage and yield a reactive **O**-type species, as suggested recently.⁷

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Supporting Information Available: Experimental, EXAFS, and DFT details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- The 1:1 TEPD–Cu(I) complex was prepared in a drybox by mixing equimolar amounts of TEPD and $[\text{Cu}(\text{CH}_3\text{CN})_n](\text{X})$ ($n = 3, 3.5, \text{ or } 4$) in CH_2Cl_2 . This clear, colorless solution was used directly. The salts $[\text{Cu}(\text{CH}_3\text{CN})_3](\text{TsO})$ and $[\text{Cu}(\text{CH}_3\text{CN})_3](\text{CH}_3\text{SO}_3)$ were prepared by adapting the procedure of Kubas, G. J.; Monzyk, B.; Crumbliss, A. L. *Inorg. Synth.* **1979**, *19*, 90–92.
- In cases where the **P:O** ratio differs significantly from 1:1, the equilibrium presumably occurs, but is difficult to detect due to the predominance of one isomer and the broadness of the UV–vis features.
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- Strong anions are detrimental to the stability of the Cu_2O_2 species. The use of PhCO_2^- was successful only in acetone at -87°C with slow addition of up to 1.0 equiv of anion per dimer. The acetate anion behaves similarly, but its **P** species is too unstable to allow a complete titration.
- The **P:O** ratio is fairly insensitive to ionic strength; only 10% of the total Cu_2O_2 concentration is converted from **P** to **O** with 200 equiv of CF_3SO_3^- added per $[(\text{TEPD})_2\text{Cu}_2\text{O}_2](\text{CF}_3\text{SO}_3)_2$ (cf. Supporting Information).
- The **P:O** ratios of $[(\text{TEPD})_2\text{Cu}_2\text{O}_2](\text{X})_2$ ($\text{X}^- = \text{SbF}_6^-$ or CF_3SO_3^-) in the more polar solvent acetone are consistently $< 10:90$, suggesting that anion association is weak in these cases. The more basic TsO^- and CH_3SO_3^- anions yield solutions of the same composition in all three solvents, suggesting that they are intimately associated with the Cu_2O_2 species.
- Scatterers differing by $Z \pm 1$ are not distinguishable in an EXAFS analysis. For these data, the resolution of such scatterers is ~ 0.12 Å.
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- Cu···S scattering at 3.4 Å has the same frequency but opposite phase as Cu···Cu scattering at 3.5 Å. This coincidence prevents independent determination of these two components. Therefore, their σ^2 parameters were constrained to have equal values during refinement.
- DFT optimizations were performed in vacuo with a B3LYP function, a 6-31G* basis set, and a broken-symmetry wave function for the singlet ground state.
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